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EXAMINER	
SINGH, ANOOP KUMAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,627	KAUFMAN ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *30-32 and 62-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29,33-61 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/15/2004; 4/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Election/Restrictions

Applicant's election of claims 1-29, 33-61 and 65 (group V) drawn to a composition for delivering a therapeutic agent to a target cell, comprising a microorganism that has on its cell surface an exogenous molecule that binds the target cell and a therapeutic agent wherein the therapeutic agent is a nucleic acid and a method for using said composition in treating neoplasia in the reply filed on April 9, 2007 is acknowledged. Applicants also elected the following species: colon cancer cell, and carcinoembryonic antigen (CEA). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 30-32 and 62-64 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/9/2007.

Claims 1-29, 33-61 and 65 directed to microorganism that has on its cell surface an exogenous molecule that binds the target cell and a therapeutic agent wherein the

therapeutic agent is a nucleic acid and method of treating neoplasia using said microorganism is under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-61 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims are directed to a method for treating neoplasia in a subject by administering a composition to treat neoplasia, wherein the therapeutic composition comprises: (a) a microorganism that has, on its cell surface, at least one exogenous molecule that binds to an antigen on the surface of a neoplastic cell in the subject; and (b) a therapeutic agent. Subsequent claims limit the neoplasia to include colon tumor and microorganism to include Salmonella, which is subsequently limited to Salmonella typhimurium VNP20009, or Salmonella typhimurium SL7207. Claims are also directed to limit the exogenous molecule to include antibody that recognizes neoplasm-specific antigen limiting to carcinoembryonic antigen (CEA). Claims 56-61 limit the therapeutic agent to include a nucleic acid that comprises one gene-silencing cassette. Claim 65 is drawn to a method of treating neoplasia in a subject by administering a composition comprising the microorganism of the invention and a therapeutic agent.

The aspects considered broad are: the breadth of microorganism that has an exogenous molecule that binds to an antigen of a target cell administered via any route,

and an agnet comprising any gene silencing expression cassette for the treatment of neoplasia of any etiology and pathology.

The nature of such invention is within the broad genera of gene delivery using a microorganism or more specifically recombinant Salmonella typhimurium (VNP20009, or SL7207) for the treatment of any neoplasia including colon cancer. However, prior art teaches that therapeutic treatment by delivering gene for the treatment is not generally enabling of due to problems with, *inter alia*, targeting and expression of transgenes at therapeutically effective level by administering compositions via any route in any specific tissue for sufficient time to elicit any therapeutic response. The art of gene delivery and therapy at the time of the filing of this application was unpredictable since numerous factors complicate the gene delivery art that is difficult to be overcome by routine experimentation. These include, the fate of DNA, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ significantly based on the vector used and the protein being produced (Ecke et al, Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). While progress has been made in recent years for *in vivo* gene transfer *in vivo* to be a desired organ continued to be unpredictable and inefficient.

As a first issue, claims 33-38, 43-61 and 65 embrace a method for treating neoplasia in a subject by administering any microorganism that expresses an exogenous molecule on its surface that binds to an antigen on the surface of neoplastic cells. As recited instant claims embrace any microorganism subsequently, limiting to attenuated microorganism for the treatment of any neoplasia subsequently limiting to colon cancer. The specification contemplates microorganism may be any alga, bacterium, fungus (including yeast), protozoan, or other microorganism (see para. 22 of the specification). The specification has exemplified generation of an attenuated Salmonella typhimurium (VNP20009 and AroA, SL7207) vector displaying anti-CEA antibody (see example 1 and 2) that may be used to test anti tumor effects of engineered vectors that express an E. coli cytosine deaminase (CD) (see example 3). It is noted that example 3 is prophetic and does not provide any guidance whether adequate infection of microorganism is achieved at the target neoplastic cell that recognizes CEA antibody expressed at the surface of microorganism to achieve therapeutic effective response. It is noted that specification describes genus of strains of bacterium, fungi that could genetically modified for the treatment of any neoplasia (see para. 23-25). Prior to instant invention, Jain et al (Exp. Opin. Biol. Ther., 2001, 1(2): 291-300) while reviewing the state of use of bacteria report that "wild type *Salmonella* cannot be used for therapeutic purpose and only attenuated mutant strains of *Salmonella* retain their tumor targeting ability and have a limited pathogenicity (see page 293, col. 1, last para.). Padlffy et al (Gene therapy, 2006, 13, 101-105) in a post filing art report problem of using bacteria for the direct gene transfer into the target

organism, organ or tissue (bactofection) that includes "the possibility of unwanted side effects related to the host–bacteria interactions. The response of the immune system might cause rapid clearance of bacteria or even autoimmune reactions. On contrary, the bacterial strains can acquire the virulence factors back and might cause serious infections" (see page 101, col. 2, para 1and 2). Padlffy et al support earlier studies of using bacteria that are attenuated to not to produce super antigens. In the instant case, claims 33-41, 43-44, 46-61 and 65 embrace any microorganism that has an exogenous molecule on its surface. Therefore, given the breadth of the claims and the guidance provided by the specification it would have required undue experimentation to make and use a composition comprising any microorganism that expresses any exogenous molecule at it surface for the treatment of neoplasia by one of skill in the art without a reasonable expectation of success.

As a second issue, instant claims are directed to a therapeutic treatment of any neoplasia subsequently limiting to colon tumor by administering any microorganism that has at least one exogenous molecule that binds to a neoplastic cell-expressing antigen. The specification does not provide any evidence that nucleic acid encoding any therapeutic protein could be delivered at therapeutic effective level to elicit a pharmacological response in specifically reducing any tumor in any subject. The specification speculates that anti-tumor effects of the engineered Salmonella typhimurium SL7207 vectors that express an E. coli cytosine deaminase (CD) may be tested using mice bearing colon adenocarcinomas (see example 3). The animal models disclosed in the specification cannot be predictive of treating any tumor or colon tumor

in any subject. Further, specification also contemplates mice with immune-system deficiencies that may demonstrate that the anti-tumor effects of SL7207/5-FC and do not depend on the presence of T or B cells (see example 3 of the specification). It appears that instant disclosure was a hypothesis, which was not reduced to practice at the time of filing of this application. In addition, mouse model comprises only transgenic or nude mice resulting in tumor formation, which cannot be extrapolated to any subject suffering from, any cancer as broadly recited in the independent claims. Gura (Science, 1997, 278: 1041-1042) describe that pharmaceutical companies often test candidate drug in animal carrying transplanted human tumors in xenograft mode. However, only few drugs that showed anticancer activity in xenograft model have made it to clinic (pp 1041, col. 1, para 3). It is not apparent from the specification how the skilled artisan would have used disclosed engineered Salmonella typhimurium (VNP20009 , SL7207l) in effectively treating different tumor of different etiology and pathology. Although human tumor xenografts implanted subcutaneously (sc) into nude mice as a predictive indicator of probable clinical activity has been validated for cytotoxic effects. Kelland et al (European Journal of Cancer, 2004, 40, 827-836) list several variables that impact on outcome; viz, site of implantation, growth properties of the xenograft and size when treatment is initiated, scheduling, route of administration and dose and the selected endpoint for assessing activity. Furthermore, Kelland emphasize that this model is valuable in cancer drug development, especially when such studies give due consideration to the above variables and are based on sound mechanistic and pharmacological principles (abstract). It is noted that, Kerbel et al (Cancer Biology &

Therapy 2: 4 suppl. 1, S134-139) also emphasize that human ectopic tumor in subcutaneous tissue sites are predictive to the outcome only if relevant, pharmacokinetic parameters are employed (pp S135, col. 2, para 1). This clearly establishes the unpredictability of the animal models extrapolated to different tumor condition especially in view of unpredictability associate with fate of DNA as evident in prior art (supra). Thus, findings in mice model with direct administration SL7207 vectors that express an E. coli cytosine deaminase cannot be directly extrapolated to effect of administering any wild type or attenuated microorganism that may also have at least one of any exogenous molecule that binds to a neoplastic cell-expressing antigen administered via any route in the treatment of any tumor in any subject. It evident that the artisan would to make a new invention in the field, Furthermore, independent claims only requires administration microorganism and as recited claims do not even require infection to target cell or binding of microorganism to the target cell. The specification also does not provide any guidance as to how studies in animal model could be extrapolated to any subject. In addition, prior art at the time of filing of this application did not provide any convincing guidance in this regard either. Because of the art, as shown above, does not disclose how the claimed genus of microorganism would be effective in any subject, the Artisan could not predict, in the absence of evidence to the contrary, that such applications as Applicant claims would be efficacious in therapeutic tumor treatment. An artisan would have to carry out extensive experimentation to make use of the invention, and such experimentation would have been undue because of the art of gene delivery *in vivo* is unpredictable and specification fails to provide any

guidance as to how the claimed method would have been practiced. The method disclosed in specification does not provide any specific guidance that sustained expression of any therapeutic gene or agent could be achieved in any subject wherein a composition comprising any microorganism expressing any exogenous molecule at the surface that binds to the target cell and any agent including nucleic acid. In spite of reports in the art as well as specification suggesting beneficial effect of nucleic acid encoding plurality of gene, numerous studies have indicated the problem of gene delivering in the treatment of any cancer. It is not apparent as how skilled artisan would carry over these inventions in any subject having any form of neoplasia or colon tumor without undue experimentation encompassing administering a composition comprising any genetically modified microorganism by administering via any route and an agent. It is also not apparent how skilled artisan without any undue experimentation, practices method as contemplated by the instant claims particularly given the unpredictability of delivering nucleic acid via microorganism as whole and unpredictability expressed in the art for the gene delivering in the treatment of cancer.

As a third issue, breadth of instant claims embraces delivering composition comprising microorganism and a gene-silencing cassette. The specification-contemplated nucleic acid may encode a gene-silencing cassette that may work at any stage including at pre-transcription silencing, transcription silencing, translation silencing, post-transcription silencing, and post-translation silencing. In a preferred embodiment, the gene-silencing cassette is a gene-knockout cassette (see para. 57 of the specification in the published application). Furthermore, specification describes

RNAi is produced *in vivo* by an expression vector containing a gene-silencing cassette coding for RNAi. However, unpredictability of attenuating /inhibiting expression of a target gene in cell by RNAi is evident in prior and post filing art. While it is recognized, that introduction of dsRNA that is targeted to a specific gene may result in attenuation /inhibition of the targeted gene, the degree of attenuation and length of the time attenuation is achieved in not predictable. Caplen et al (Gene 2000, vol. 252, 95-105) provide evidence of the unpredictability of dsRNA attenuation /inhibition of targeted gene in vertebrate cell in vitro. Transient transfection of dsRNA to the βgal trasngene into 293 and BHK31 cells resulted either in no effect or a non-specific decrease in gene expression (pp102; Figure 7 A and B). This is further supported by studies of Novina et al (Nature 2004, Vol.430:161-164) indicating that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph). Furthermore, Paroo et al. (Trends in Biotechnology 2004, 22(8): 390-394) describes, "developing siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles (also see Ecke et al, supra). However, the duplex nature of siRNA introduced an additional layer of complexity. Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph). The specification fails to provide adequate guidance to an enabled method for treatment of any neoplasia in any subject by delivering an gene silencing cassette to

overcome the art recognized unpredictability in a method of treating neoplastic condition, it would require undue experimentation for an Artisan to make and use the claimed invention without reasonable expectation of success.

As a fourth issue, claims embrace microorganism that displays exogenous molecule that binds to an antigen on the surface of target cell and an agent. The specification teaches generation of an attenuated Salmonella typhimurium (VNP20009 and AroA, SL7207) vector displaying anti-CEA antibody (see example 1 and 2). The specification describes molecule may be any peptide (a polypeptide), saccharide, lipid, a peptidoglycan, or any combination of peptides, saccharides, and lipids (see paragraph 37). Furthermore, specification contemplates "polypeptide" includes proteins, polypeptides, peptides, and variants preferably have greater than about 75% homology with the naturally-occurring polypeptide and variants may be substitutional, insertional, or deletional variants. The variants may also be chemically modified derivatives: polypeptides which have been subjected to chemical modification, but which retain the biological characteristics of the naturally-occurring polypeptide (see para. 38 of the published application. Prior to instant invention, Davis, (New Biologist, 1990, 2(5), 410-419) teaches that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid. These observations are further supported by the studies of

Skolnick et al (Trends in Biotech, 2000,18, 34-39) describing, "..sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (abstract). Skolnick further states that "knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (page 36, column 1, box 2). It is emphasized that identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Rudinger in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). Therefore, It is apparent from the cited art that biological function of a protein was unpredictable from amino acid sequence at the time of the invention and even same short stretch of amino acid sequence could show diverse biological functions while surrounded by different background amino acid sequences. In the instant case, claims are directed to an exogenous molecule that may be any polypeptide or antibody. The specification does not adequately provide structure function relationship of adequate number of molecule that would be capable of performing any such function to bind to the target region. The breadth of these claims embraces numerous different unidentified proteins, having diverse biological effect to

treat different tumor. Absent of evidence to the contrary, it is not clear that these elements or any molecule or protein or antibody capable of binding to a target cell expressing an antigen would be functional in a method of treating any neoplasia in the same manner as they have been demonstrated in the instant application. An artisan would have to perform undue experimentation to empirically test different molecule, protein or antibody that are capable of binding to a target cell expressing an antigen for targeting neoplastic cells for the treatment of neoplasia as broadly recited in the instant claims.

As a final issue, instant claims embrace treating a tumor by administering via any route a composition comprising a microorganism that express any exogenous molecule on its surface that binds to an antigen that expresses on tumor cells and any therapeutic agent which is a nucleic acid. The specification describes that efficiency of plasmid transfer, and the resulting therapeutic effect of any given gene, might be substantially enhanced by directing Salmonella straight into epithelial cells (see example 2) and composition may be given orally and intravenously (see example 3). It is noted that specification teaches that route of administration would depend on the nature of the tumor and the kind of microorganisms or cells contained in the pharmaceutical composition. It has been difficult to predict the efficacy and outcome of transduced therapeutic genes because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo*. The transduction of target cells represents the first critical step in any gene-based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery microorganism or

engineered bacterial vectors. In addition, besides the limitations in gene transfer the problem to selectively target cells *in vivo* is still one of the most difficult obstacles to overcome. For example, McCluskie et al teaches that the route of delivery of DNA vaccine influences immune responses in laboratory animals (McCluskie et al (1999) Mol. Med. 5:287-300; Abstract). Specifically, in one study McCluskie et al observed lack of response to non-injected routes of administration of DNA based vaccines, such as oral routes, sub lingual, inhalation and vaginal wall due to variation in transfection efficiency (Abstract). There have also been the problem of immune and cytokine responses against the delivery vehicle obstructing delivery of gene therapies. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan would have practiced the claimed method in any subject including humans by administering compositions via any route to elicit a pharmacological response for sustained period.

In conclusion, in view of breadth of the claims and absence of adequate showing by applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach an *in vivo* method of tumor treatment by administering via any route any microorganism that has one exogenous molecule at its surface and an agent for the treatment of any neoplasia. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of the gene

delivery was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

Claim Rejections - 35 USC § 112-Written Description

Claims 1-29, 33-61 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim embraces a microorganism that has on its surface at least one exogenous molecule that binds to an antigen on the surface of the target cell. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116. In analyzing whether the written description requirement is met for the genus claim, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the exogenous molecule that binds to an antigen on the surface of the target cell, encompassed within the genus of molecule that are

capable of binding to an antigen. The specification describes molecule may be any peptide (a polypeptide), saccharide, lipid, a peptidoglycan, or any combination of peptides, saccharides, and lipids (see paragraph 37). In addition, instant specification contemplates "polypeptide" includes proteins, polypeptides, peptides, and variants preferably have greater than about 75% homology with the naturally-occurring polypeptide and variants may be substitutional, insertional, or deletional variants. The variants may also be chemically modified derivatives: polypeptides which have been subjected to chemical modification, but which retain the biological characteristics of the naturally-occurring polypeptide (see para. 38 of the published application). Based upon the prior art there is expected to be structure or peptide sequence variation that is capable to bind to an antigen. The specification describes exogenous polypeptide include gA, IgD, IgE, IgG, IgM, and single-chain antibodies), fragments of antibodies (including Fab fragments, such as scFv (see paragraph 39). The specification has exemplified a composition comprising attenuated *Salmonella Typhimurium* vector displaying anti-CEA antibody to target CEA antigen expressed on color cancer cells (see example 1, 2) and only CEA-specific scFv molecules were folded properly and functional (see figure 4). However, specification fails to provide any particular structure to function/activity relationship in this single disclosed species for use in the invention for genus of sequence or fragments or molecule that is capable of binding to an agent on the surface of a target cell except those exemplified in the instant application. It is emphasized that an addition or deletion of amino acid from critical region in polypeptide as contemplated in the specification may not show contemplated biological activity. This

is particularly critical as protein is highly dependent on the overall structure of the protein itself and the primary amino acid sequence determines the conformation of the protein. This is also evidenced by studies of Ngo et al that disclose addition or deletions, which are critical to maintain the protein structure/function, will require guidance. The mere identification of critical regions would not be sufficient, as encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (Ngo et al., 1994, The protein Folding Problem and Tertiary Structure Prediction, pp491-495). Thus, it is apparent that a minor structural difference in compositions could result in substantially different activities. The specification however has not disclosed the addition or deletion of any region that would be functional to bind to an antigen on the surface of the target cell. The claimed invention as a whole is not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics. Inc.*, 48 USPQ2d 1641, 1646 (1998). The specification fails to describe what structure or sequence of molecule other than exemplified in the specification fall into the genus that has contemplated biological activity of binding to an antigen on the surface of a target cell. The skilled artisan cannot envision the detailed chemical structure of the all the molecule or sequences showing contemplated biological activity, and therefore conception are not achieved until

reduction to practice has occurred, regardless of the complexity or simplicity of the composition.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 UsPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In view of the above considerations, one of skill in the art would not recognize that applicant was not in possession of the necessary common features or attributes possessed by member of the genus of molecule that binds to an antigen on the surface of a target cell, other than the ones exemplified in the specification. Therefore, Applicant was not in possession of the genus of microorganism that has at least any one exogenous molecule on it surface as encompassed by the claims. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-27 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Bereta et al (American association Cancer Research , 2002, vol. 43, April 6-10, abstract 3288, page 663, IDS) .

Bereta et al teach an attenuated strain of Salmonella typhimurium (Aro A, SL7207) which expresses a single chain Fv antibody specific for CEA at the surface. It is noted that the bacterium further comprises a plasmid (pcDNA3.1/GFP) encoding a reporter gene GFP. Bereta et al also contemplate testing the plasmid in murine colon tumor cells transduced with LXSN/CEA retroviral vector and a human CEA transgenic mouse model. The genetically modified Salmonella typhimurium disclosed by Bereta et al and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound

basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Accordingly, Bereta et al anticipates claims 1-27 and 29.

Claims 1-4, 6-7, 9-11, 25-27 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Francisco et al (Proc Natl Acad Sci U S A. 1993; 90(22): 10444-8, IDS).

Francisco et al (Proc Natl Acad Sci U S A. 1993; 90(22): 10444-8) teach a composition comprising a functional scFv antibody fragment attached to the outer surface of E. coli that is capable to bind an antigen with high affinity that also comprises a construct comprising chloramphenicol-resistance gene (see material and methods page 10444, col. 2, para 1 and 10445, col. 2, para. 2 and 3) meeting the claim limitation. It is noted that Francisco et al also disclose scFv antibody fragment specific for digoxin on the surface of E. coli. Accordingly, Francisco et al anticipate claims 1-4, 6-7, 9-11, 225-27 and 29.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to

identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-29, 33-61 and 65 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-29, 33-61 and 65 of copending Application No. 11/213499 (US patent publication no. 20060083716). Claims in instant applications are directed to a method for treating neoplasia in a subject by administering a composition to treat neoplasia, wherein the therapeutic composition comprises: (a) a microorganism that has, on its cell surface, at least one exogenous molecule that binds to an antigen on the surface of a neoplastic cell in the subject; and (b) a therapeutic agent. Subsequent claims limit the tumor to include colon tumor and microorganism to include Salmonella, which is subsequently limited to Salmonella typhimurium VNP20009, or Salmonella typhimurium SL7207. Claims are also directed to limit the exogenous molecule to include antibody that recognizes neoplasm-specific antigen limiting to carcinoembryonic antigen (CEA). Claims 56-61 limits the therapeutic agent to include a nucleic acid that comprises one gene-silencing cassette. Claims are also drawn to further limit the plasmid to include expression plasmid that is transferred into a neoplastic cells. Claims 65 is drawn to a method of treating neoplasia in a subject by administering a composition comprising the microorganism of the invention and a

therapeutic agent. While claims in copending application No. 11/213499 (US patent publication no. 20060083716) are same as one recited in instant application including a composition for delivering an agent to a target cell, comprising: (a) a microorganism that has, on its cell surface, at least one exogenous molecule that binds to an antigen on the surface of a target cell; and (b) an agent and a method of for treating neoplasia in a subject in need of treatment, comprising composition of the invention.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dillon et al (US Patent no 5, 395,750, dated 3/7/1995) teaches method of producing protein and expressing on the surface of microorganism that binds to predetermined antigen.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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